REMARKS

In the Office Action received August 13, 2003, claims 1-49 were pending, claims 1-25 and 28 were rejected, and claims 26, 27 and 29-49 were withdrawn from consideration. The Examiner stated that based on the Applicant's traversal the restriction between Group I and Group II had been reconsidered and withdrawn, but that the traversal of the restriction between group VI and VII was not found persuasive and was made final.

In response thereto, claims 25-27 and 29-49 have been cancelled and claims 1, 5-6, 11, 14, 17, 20-21, 23, and 28 have been amended. Support for the claim amendments can be found in the Specification on page 5, lines 5-10; page 11, lines 3-6; page 13, line 27 through page 14, line 2; page 21, lines 1-8; page 15, lines 1-9; page 17, lines 19-24; and Example 1. In addition, new claims 50-53 have been added to more completely claim the invention. Support for new claims 50-53 can be found in the Specification in Example 1. None of the amendments set forth herein constitute the addition of new matter. Upon entry of these amendment, claims 1-24, 28, and 50-53 remain pending for the Examiner's consideration. Reconsideration of the application in light of the above amendments and the following remarks is respectfully requested.

A. Rejections under 35 U.S.C. § 112, second paragraph, addressed

Claims 1-25 and 28 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. First, the Examiner asserts that the metes and bounds encompassed by "removing a binding site" is not clear and the specification does not provide for a way of determining at what point enough binding site is removed to be able to "eliminate or reduce" infection. Next, the Examiner asserts that while the claims are drawn to a method of "eliminating or reducing the infection in a biological material", they do not set out sequential method steps needed to achieve the method. This rejection is respectfully traversed.

Independent claims 1, 21 and 23 have been amended herein to clarify the claim language. Specifically, the claims now recite a method of eliminating or reducing greater than about 75% of infectious agent binding sites present in a biological material. The method involves contacting the biological material two or more times with an aliquot preparation that removes the binding site from the material so that the infectious agent cannot bind to the biological material. Independent claim 21 is specifically directed to a method of removing an

unwanted protein binding site, and independent claim 23 is specifically directed to removing a protein or polysaccharide that is a binding site for the infectious agent.

Thus, the claims now clearly recite that the method comprises removing at least about 75% of the binding sites for the infectious agent. As stated in the Specification on page 16, lines 27-30, by removing the binding site for the protein, the actual protein can be more easily removed by simple washing, or is itself removed as it remains associated with the binding site. Thus, when the preparation no longer removes additional binding site, an endpoint is reached, which is indicative of the amount of preparation necessary to eliminate or reduce infectious agent contamination (See Specification at page 5, lines 5-18; page 13, line 13 through page 14, line 2; and page 15, lines 5-9). In addition, Example 1 describes one embodiment of this invention for removing phospholipid binding sites. As shown the Table on page 28, the first bioburden reduction results in an average removal of about 75% of the phospholipid binding sites, and the second bioburden achieves about 98% removal of the phospholipid binding sites. Further, the terminal liquidation sterilization step does not remove additional phospholipids.

Thus, it is asserted that the amendments presented in independent claims 1, 21 and 23 clearly indicate how much of the binding site must be removed in order to be effective. i.e., "at least about 75% of the binding site". It is further asserted that the amendments clarify that the binding site is indeed specific for the particular infectious agent to be removed from the biological material. Finally, the claim amendments address the Examiner's concerns with the method steps required to reduce or eliminate infection in a biological material, in that the claims now recite a method for eliminating or reducing infectious agent contamination in a biological material and further recite the steps for doing so. Withdrawal of this Section 112, second paragraph rejection is respectfully requested.

B. Rejections under 35 U.S.C. § 102(b) addressed

Various combinations of claims 1-25 and 28 were rejected as being anticipated by Lee et al., Nashef, Abraham et al., Girardot et al., Mirsch et al., Vyavahare et al., or Cunanan et al. for the reasons discussed below. As the Examiner is aware, the CAFC has stated that anticipation requires the presence in a single prior art reference of the disclosure of each and every element of the claimed invention, arranged as in the claim. *Lindemann Maschinenefabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1458 (Fed. Cir. 1984); *Altco Standard Corporation v. Tennessee Valley Authority*, 1 USPQ 1337, 1341 (Fed.

Cir. 1986); 774 F.2d 1082 (Fed. Cir. 1985). It is asserted that the above-listed references do not disclose every element of claims 1-25 and 28 as amended herein or every element of newly presented claims 50-55. Accordingly, the Section 102 rejections are respectfully traversed for the reasons discussed below.

1. Lee fails to meet Applicants' claim elements of (a) eliminating or reducing about 75% of binding site for the infectious agent; (b) washing the tissue two or more times fresh aliquots of the same solution; and (c) measuring the amount of binding agent removed.

Claims 1-15, 19, 21, 23, 25 and 28 were rejected under 35 U.S.C. § 102(b) as being anticipated by Lee et al. (U.S. Patent No. 6,008,292). The Examiner first asserts that "any method that removes protein or cellular debris from a biological material would fall within the scope of the claim by removing the undefined binding sites". The Examiner then asserts that Lee discloses a method of preparing collagenous biological material by treating the tissue with Denacol and 20% ethanol as well as treating tissue with a mixture of glutaraldehyde, ethanol and Tween-80 and therefore anticipates the present invention. This rejection is respectfully traversed.

It is asserted that Lee does not expressly or inherently describe all of the elements set forth in claims 1-15, 19, 21, 23, 25 and 28. Independent claim 1 as amended now recites a method of eliminating or reducing greater than about 75% of infectious agent binding sites present in a biological material. The method involves contacting the biological material two or more times with an aliquot preparation that removes the binding site from the material so that the infectious agent cannot bind to the biological material. Independent claim 21 has been amended in a similar manner to recite a method of removing greater than about 75% of an unwanted protein from a biological material, which comprises contacting the biological material one or more times with a preparation that removes the unwanted protein's binding site from the material so that the unwanted protein cannot bind to the biological material. Finally, independent claim 23 has been amended in a manner similar to claim 1 to recite a method of eliminating or reducing greater than about 75% of a binding site in a biological material, wherein the binding site is a protein or polysaccharide. All of the methods require washing the material two or more times with a fresh aliquot of a preparation, and measuring the amount of binding site in each aliquot. Further, each washing uses a fresh aliquot of the preparation. Thus, to anticipate any of claims 1, 21 or 23 or the claims that depend therefrom, Lee must disclose a method of eliminating or reducing greater than about 75% of

infectious agent binding sites in a biological material by washing the material two or more times with a fresh solution.

In contrast to Applicants' claimed methods, Lee is directed to a method for inhibiting calcification of a fixed collagenous biological tissue by treating the fixed tissue with Decanol (ethylene glycol diglycidyl ether) and ethanol for 120 hours. As a control, Lee treats fixed tissue with a mixture of gluteraldehyde, ethanol and Tween 80. After measuring only the calcium content of the tissue samples following treatment, Lee concludes that ethylene glycol diglycidyl ethers are capable of mitigating tissue calcification (see also Lee's claim 1). Thus, Lee was only concerned with identifying an agent that would prevent calcification rather than identifying a method of removing binding sites on the biological material. Therefore, Lee fails to teach or even suggest all the elements of claims 1-15, 19, 21, 23, 25 and 28, which require washing the material two or more times with an aliquot of a preparation, and measuring the amount of binding site in each aliquot until greater than about 75% of the binding sites have been removed from the material. Accordingly, Lee does not anticipate these claims. Further, since one skilled in the art would not look to Lee for guidance on how to remove infectious agent binding sites (e.g., in order to prevent or inhibit infectious agent contamination), Lee does not render the present invention obvious. Withdrawal of this rejection over Lee is respectfully requested.

2. Nashef fails to meet Applicants' claim elements of (a) eliminating or reducing about 75% of binding site for the infectious agent and (b) measuring the amount of binding agent removed.

Claims 1-15, 17, 19, 21, 23, 25 and 28 were rejected under 35 U.S.C. § 102(b) as being anticipated by Nashef (U.S. Patent No. 4,729,139). The Examiner asserts that Nashef discloses utilizing a disinfecting solution for the processing of bioprosthetic tissue comprising formaldehyde, ethanol and Tween-80, and further asserts that since ethanol and Tween are know to be capable of solubelizing phospholipids and formaldehyde is a well-known sterilization agent, Nashef anticipates the present invention. This rejection is respectfully traversed.

It is asserted that Nashef does not expressly or inherently describe all of the elements set forth in claims 1-15, 17, 19, 21, 25, 25 and 28. As stated in Section B(1), the claims as amended herein recite methods to of eliminating or reducing greater than about 75% of infectious agent binding sites present in a biological material, comprising washing the

material two or more times with a fresh aliquot of a preparation, and measuring the amount of binding site in each aliquot.

In contrast to Applicants' claimed methods, Nashef discloses a method for incorporating a polymer into a biological tissue to inhibit calcification. The method involves fixing the tissue with gluteraldehyde, coupling the tissue with a coupling agent such a diamine, contacting the coupled tissue with a first monomer solution (e.g., a solution containing acrylic acid) and then exposing the tissue to a polymerization initiator, and then contacting the tissue with a second monomer solution under polymerization conditions. Nashef briefly mentions sterilizing the tissue prior to this sequence by contacting the tissue with a formaldehyde/ethanol/Tween solution. However, Nashef is silent as to the sterilization conditions or whether the sterilization conditions even remove any infectious binding sites. In addition, Nashef does not teach or even suggest that the sterilization step involves measuring the amount of infectious agent binding site that was removed from the tissue after contacting the tissue with the sterilization solution.

Since Nashef was only concerned with identifying method for preventing calcification rather than identifying a method of preventing infectious agent contamination of a tissue, Nashef fails to teach or even suggest all the elements of claims 1-15, 17, 19, 21, 23, 25 and 28, which require washing the material two or more times with an aliquot of a preparation, and measuring the amount of binding site in each aliquot until greater than about 75% of the binding sites have been removed from the material. Accordingly, Nashef does not anticipate these claims. Further, since one skilled in the art would not look to Nashef for guidance on how to remove infectious agent binding sites (e.g., in order to prevent or inhibit infectious agent contamination), Nashef does not render the present invention obvious. Withdrawal of this rejection over Nashef is respectfully requested.

3. Abraham fails to meet Applicants' claim elements of (a) washing the biological material with two or more aliquots of the same solution; (b) measuring the amount of binding sites in each aliquot; and (c) maintaining the structural integrity of the biological material.

Claims 1-4, 18 and 20-25 were rejected under 35 U.S.C. § 102(e) as being anticipated by Abraham et al. (U.S. Patent No. 6, 599,690). The Examiner asserts that Abraham discloses a method of cleansing/treating tissue to remove non-collagenous components by treatment with alkali, chelating agents and acids. The Examiner further asserts that because

cellular material and protein is removed in Abraham's processing steps, infectious agents and binding site for the infectious agent are removed in the process as well, and thus concludes that Abraham anticipate the present invention.

It is asserted that Abraham does not expressly or inherently describe all of the elements set forth in claims 1-4, 18 and 20-25. The claims as amended herein recite the claims as amended herein recite methods to of eliminating or reducing greater than about 75% of infectious agent binding sites present in a biological material, comprising washing the material two or more times with a fresh aliquot of the same solution, and measuring the amount of binding site in each aliquot. Further, independent claims 1, 21 and 23 have been amended to recite that the method maintains the structural integrity of the biological material, i.e., the process removes the binding sites but does not render the biological material acellular.

In contrast to Applicants' claimed methods, Abraham is directed to a method of treating collagenous tissues to remove all non-collagenous components -- i.e., to ultimately obtain a collagen matrix (an acellular material). Abraham's method involves multistep washings, wherein each washing uses a different type of washing solution (e.g., a basic chelating reagent solution, an acidic solution, a salt solution, etc. - see Abraham's Example 1). Further, since the goal of Abraham's method is to remove all components other than collagen from the tissue, Abraham is silent with respect to measuring the amount of these components, let alone a measuring the amount of binding site for a particular infectious agent, in the washing solutions.

Accordingly, Abraham fails to teach or even suggest all the elements of claims 1-4, 18 and 20-25, which require washing the material two or more times with a fresh aliquot of the same, and measuring the amount of binding site in each aliquot until greater than about 75% of the binding sites have been removed from the material. Accordingly, Abraham does not anticipate these claims. Further, since one skilled in the art would not look to Abraham for guidance on how to remove infectious agent binding sites (e.g., in order to prevent or inhibit infectious agent contamination), Abraham does not render the present invention obvious. Withdrawal of this rejection over Abraham is respectfully requested.

4. Giradot fails to meet Applicants' claim elements of (a) eliminating or reducing about 75% of binding site for the infectious agent; (b) washing the biological material two or

more times with fresh aliquots of the same solution; and (c) measuring the amount of binding agent removed.

Claims 1, 3, 4, 11, 19, 23, 25, and 28 were rejected under 35 U.S.C. § 102(e) as being anticipated by Girardot et al. The Examiner states that Girardot discloses a process of sterilization of biological tissue using EDC, Hepes, NaCl, and isopropyl alcohol at concentrations effective to kill microorganisms, and therefore asserts that Girardot anticipates the present invention. This rejection is respectfully traversed.

It is asserted that Girardot does not expressly or inherently describe all of the elements set forth in claims 1, 3, 4, 11, 19, 23, 25, and 28. As stated in Section B(1), the claims as amended herein recite methods to of eliminating or reducing greater than about 75% of infectious agent binding sites present in a biological material, comprising washing the material two or more times with a fresh aliquot of a preparation, and measuring the amount of binding site in each aliquot.

In contrast to Applicants' claim methods, Girardot teaches a method of sterilizing a tissue by killing microorganisms contained in the tissue. The method involves adding a coupling agent such as EDC to a fixed tissue that forms amide bonds with proteins and enzymes in the microorganisms, thereby killing the microorganisms. The alcohol is added to assist the coupling agent in effectively penetrating the cell walls of the microorganisms. Clearly the goal of Girardot was not to find a method of removing infectious agent binding sites, but rather to kill the microorganisms contained in the tissue. Thus, Girardot is not only silent with respect to washing the tissue two or more times with fresh aliquots of the same solution, but further Girardot does not teach or suggest that the sterilization step involves measuring the amount of binding sites contained in the aliquots after the washing step. Accordingly, Girardot does not teach or even suggest all the elements of claims 1, 3, 4, 11, 19, 23, 25, and 28, and therefore does not anticipate these claims. Further, since one skilled in the art would not look to Girardot for guidance on how to remove infectious agent binding sites (e.g., in order to prevent or inhibit infectious agent contamination), Girardot does not render the present invention obvious. Withdrawal of this rejection over Girardot is respectfully requested.

5. Mirsch fails to meet Applicants' claim elements of (a) eliminating or reducing about 75% of binding site for the infectious agent; (b) washing the tissue two or more times fresh aliquots of the same solution; and (c) measuring the amount of binding agent removed.

Claims 1-4, 14-16, and 18-25 were rejected under 35 U.S.C. § 102(a) or (e) as being anticipated by Mirsch et al. (U.S. Patent No. 6,121,041). The Examiner asserts that Mirsch discloses a method of decellularizing a bioprosthetic issue and as a result the binding sites found in the cellular martial are also removed. From this the Examiner concludes that Mirsch anticipates the present invention. This rejection is respectfully traversed.

It is asserted that Mirsch does not expressly or inherently describe all of the elements set forth in claims 1-4, 14-16, and 18-25. As stated in Section B(1), the claims as amended herein recite methods to of eliminating or reducing greater than about 75% of infectious agent binding sites present in a biological material, comprising washing the material two or more times with a fresh aliquot of a preparation, and measuring the amount of binding site in each aliquot.

In contrast to Applicants' claimed methods, Mirsch discloses a method of inoculating a tissue with a solution containing microorganisms, wherein the microorganisms are selected to produce compounds that process the tissue. Mirsch states that the tissue can subsequently be treated to remove or inactivate the microorganisms by "ionizing radiation, ultraviolet irradiation, antibiotics and chemical exposure" (see Mirsch claim 1). However, not only is Mirsch silent with respect to a method of removing binding sites for the microorganisms, but in addition Mirsch does not provide any further details of the sterilization step, and clearly does not teach or even suggest washing the material two or more times with an aliquot of a preparation, and measuring the amount of binding site in each aliquot until greater than about 75% of the binding sites have been removed from the material as set forth in the present claims. Accordingly, Mirsch does not anticipate claims 1-4, 14-16, and 18-25. Further, since one skilled in the art would not look to Mirsch for guidance on how to remove infectious agent binding sites, Mirsch does not render the present invention obvious. Withdrawal of this rejection over Lee is respectfully requested.

6. Vyavahare fails to meet Applicants' claim elements of (a) washing the tissue two or more times fresh aliquots of the same solution; (b) measuring the amount of binding agent removed; and (c) maintaining the structural integrity of the tissue.

Claims 1-4, 14, 15, and 17 were rejected under 35 U.S.C. § 102(b) as being anticipated by Vyavahare et al. (Circulation, 1997). The Examiner states that Vyavahare discloses the removal of phospholipid from a glutaraldehyde fixed bioprosthetic tissue using

an ethanol wash, and thus asserts that Vyavahare anticipates the present invention. This rejection is respectfully traversed.

It is asserted that Vyavahare does not expressly or inherently describe all of the elements set forth in claims 1-4, 14, 15, and 17. As stated in Section B(1), the claims as amended herein recite methods to of eliminating or reducing binding sites present in a biological material by washing the material two or more times with a fresh aliquot of a preparation, and measuring the amount of binding site in each aliquot. Further, the claims have been amended to clarify that the method maintains the structural integrity of the tissue.

In contrast to Applicants' invention, Vyavahare discloses a method for preventing calcification of bioprosthetic heart valves using ethanol pretreatments. The method involves soaking the tissue in ethanol at concentrations greater that 60% for 24 hours to remove membrane lipids and to induce collagen structural changes (page 479, second column, first paragraph; page 480, first column, third paragraph; page 481, second column, second full paragraph). The extreme ethanol conditions cause "significant changes in collagen structure. Specifically, the infrared amide I region demonstrated a prominent and irreversible change" (page 484, first column, first paragraph). Clearly the Vyavahare method does not maintain the structural integrity of the tissue as required by claims 1-4, 14-15 and 17. Further, Vyavahare does not teach or even suggest a method of removing binding sites by contacting the tissue two or more times with fresh aliquots of a solution and measuring the amount of binding sites in the aliquots after each washing.

Accordingly, since Vyavahare does not teach every element of 1-4, 14-15 and 17, Vyavahare does not anticipate these claims. Further, since one skilled in the art would not look to Vyavahare for guidance on how to remove infectious agent binding sites, Vyavahare does not render the present invention obvious. Withdrawal of this rejection over Vyavahare is respectfully requested.

7. Cunanan fails to meet Applicants' claim elements of

Claims 1-15, 17-25 and 28 were rejected under 35 U.S.C. § 102(a) or (e) as being anticipated by Cunanan et al. (U.S. Patent No. 6,214,054) as evidenced by Vyavahare et al. The Examiner states that Cunanan discloses a method of preparing bioprosthetic tissue using a combination of formaldehyde, ethanol and Tween for the processing for the tissue, and Vyavahare provides evidence that ethanol treatment is effective at removing phospholipids

from tissue. Thus, the Examiner asserts that Cunanan anticipates the present invention. This rejection is respectfully traversed.

It is asserted that Cunanan does not expressly or inherently describe all of the elements set forth in claims 1-15, 17-25 and 28. As stated in Section B(1), the claims as amended herein recite methods to of eliminating or reducing binding sites present in a biological material by washing the material two or more times with a fresh aliquot of a preparation, and measuring the amount of binding site in each aliquot.

In contrast to Applicants' invention, Cunanan discloses a method for preparing a bioprosthesis in a manner that mitigates post-implantation calcification of the bioprosthesis. The method involves immersing the tissue in a denaturant/surfactant/crosslinking agent mixture for 2 to 24 hours and then rinsing the tissue. However, Cunanan does not teach or even suggest washing the tissue two or more times with fresh aliquots of the same solution and further does not teach or suggest measuring the amount of binding sites present in the aliquots after each washing. In addition, Cunanan does not teach removing at least about 75% of the binding sites from the tissue. As shown in Applicants' Example 1, washing the tissue with a solution such as a mixture of a denaturant/surfactant/crosslinking agent does not remove more than about 75% of phospholipid binding sites, and therefore more than one washing is necessary to achieve removal of greater than about 75% of the binding sites as required by claims 1-15, 17-25 and 28.

Accordingly, since Cunanan does not teach every element of 1-15, 17-25 and 28, Cunanan does not anticipate these claims. Further, since one skilled in the art would not look to Cunanan for guidance on how to remove infectious agent binding sites, Cunanan does not render the present invention obvious. Withdrawal of this rejection over Cunanan is respectfully requested.

C. Obviousness-type double patenting rejection addressed

Claims 1-15, 17-25 and 28 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 6,214,054 in view of Vyavahare et al. The Examiner asserts that although the conflicting claims are not identical, they are not patentably distinct from each other because the method disclosed in U.S. Patent No. 6,214,054 will result in the removal of phospholipid from the fixed bioprosthetic tissue, as evidence by Vyavahare et al. were phospholipid removal was

achieved with ethanol treatment of glutaraldehyde fixed bioprosthetic tissue. This rejection is respectfully traversed.

The arguments presented above in Section B(7) demonstrating the novelty and nonobviousness of the present invention over Cunanan pertain to this rejection and are incorporated herein by reference. As discussed, the clearly distinguish the present invention over Cunanan in several respects. First, the present invention provides a method of removing greater than about 75% of the infectious agent binding sites from the tissue. Second, the present invention requires that the tissue be washed two or more times with fresh aliquots of a solution in order to achieve greater than about 75% removal. Third, the present invention requires that the amount of binding sites removed by the aliquots be measured after each wash step. Therefore, even if the teachings of Cunanan were combined with the teachings of Vyavahare, the combination still would not teach or suggest the method set forth in claims 1-15, 17-25 and 28 as amended. Withdrawal of this rejection is respectfully requested.

CONCLUSION

Accordingly, in view of the above amendments and remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at the telephone number listed below. The fee associated with the filing of a two month time extension accompanies this response. No additional fee is believed due as a result of filing this Amendment. However, should any additional fees be due the Examiner is authorized to charge Deposit Account No. 50-1123.

Respectfully submitted,

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Dated

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